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Bridging NCL research gaps☆

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ABSTRACT

The neuronal ceroid lipofuscinoses, collectively called NCLs, are rare and fatal lysosomal storage diseases that mainly affect children. Due to the fact that NCLs are both rare and heterogeneous (mutations in thirteen different genes) significant gaps exist in both preclinical and clinical research. Altogether, these gaps are major hurdles to bring therapies to patients while the need for new therapies is urgent to help them and their families. To define gaps and discuss solutions, a round table discussion involving teams and different stake holders took place during the 14th International Conference on Neuronal Ceroid Lipofuscinoses (Batten Disease) in Cordóba, Argentina. Topics covered by the teams and their leaders (in parentheses) included basic and translational research gaps with regard to large animal models (I. Tammen, D.N. Palmer), human NCL pathology and access to human tissue (J.D. Cooper, H.H. Goebel), rare NCLs (S. Hofman, I. Noher), links of NCLs to other diseases (F.M. Platt), gaps between clinic and clinical trials (H. Adams, A. Schulz), international collaborative efforts working towards a cure (S.E. Mole, H. Band) perspectives on palliative care from patient organizations (M. Frazier, A. West), and issues NCL researchers face when progressing to independent career in academia (M. Bond). Thoughts presented by the team leaders include previously unpublished opinions and information on the lack of understanding of disease pathomechanisms, gene function, assays for drug discovery and target validation, natural history of disease, and biomarkers for monitoring disease progression and treatment effects. This article is not intended to review the NCL literature. It includes personal opinions of the authors and it provides the reader with a summary of gaps discussed and solutions proposed by the teams. This article is part of a Special Issue entitled: Current Research on the Neuronal Ceroid Lipofuscinoses (Batten Disease).

1. Introduction

Significant gaps exist in research of the neuronal ceroid lipofuscinoses (NCLs), often collectively referred to as Batten disease [1]. The NCLs are caused by mutations in thirteen different genes (Mole and Cotman, this issue) and are classified as lysosomal storage diseases (LSDs), a group of over 50 rare inherited metabolic disorders that result from defects in lysosomal function [2]. The incidence of NCLs varies from type-to-type and from country-to-country [3]. Together, mutations in CLN1, CLN2, and CLN3 account for the vast majority of NCL cases, those in CLN5, CLN6, CLN7, and CLN8 for the vast majority of rare NCL cases, while mutations in CLN4, CLN10, CLN11, CLN12, CLN13, and CLN14 account for only a very small proportion of all NCL cases (http://www.ucl.ac.uk/ncl/SummaryTableMay2015.htm, Mole and Cotman, this issue) [3]. Although grouped as NCLs because of similarities in pathology and clinical manifestations (Radke et al., this issue; Cooper et al., this issue), the NCLs are caused by mutations in genes which proteins have thus far shown little or no cross-talk at a molecular level (Cárcel-Trullols et al., this issue) [4]. It is therefore not evident how therapies developed for one NCL form may translate to another form. From a therapy perspective, the NCLs caused by mutations in genes encoding soluble lysosomal enzymes (CLN1, CLN2, CLN10, and CLN13) are considered targets for enzyme replacement therapy (ERT) and gene therapy [5]. For CLN2, a phase 1/2 ERT open-label dose-escalation study is ongoing in patients with late-infantile neuronal ceroid lipofuscinosis (CLN2) disease, to evaluate safety, tolerability, pharmacokinetics, and efficacy of intracerebroventricular delivered recombinant tripeptidyl peptidase I (ClinicalTrials.gov Identifier: NCT01907087). CLN2 gene delivery is also under investigation (clinical trials.gov Identifier: NCT01161576) [6]. There is hope that CLN5, which is not known to encode an enzymatic function (Cárcel-Trullols et al., this issue), might also be deliverable via gene therapy as suggested by preclinical results in CLN5-deficient sheep (Palmer et al., this issue). Finding therapeutic entry points for NCLs caused by mutations in CLN3, CLN6, CLN7, and CLN8 is much more

Abbreviations: NCL, neuronal ceroid lipofuscinosis; LSD, lysosomal storage disease; ERT, enzyme replacement therapy; ER, endoplasmic reticulum; PoC, proof-of-concept; iPS cell, induced pluripotent stem cell; PD, Parkinson's disease; NPC, Niemann–Pick type C; SLOS, Smith–Lemli–Opitz syndrome; FTLD, frontotemporal lobe degeneration; JNCL, juvenile NCL; EU, European Union; DEM-CHILD, dementia in childhood; EEG, electroencephalography; MRI, magnetic resonance imaging.

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challenging as these genes all encode transmembrane (TM) proteins. They seem located either mainly in the endoplasmic reticulum (ER), like CLN6 and CLN8, and/or the endolysosomal compartments, like CLN3 (Cárcel-Trullols et al., this issue) [4,7]. Therefore, research gaps and hurdles in the translation of therapies to the clinic vary considerably from one NCL form to another.

Nonetheless, there are gaps that are common to most of the NCLs, such as the lack of an in-depth understanding of the natural history of the disease [8], which is one of the prerequisites to successfully pave the road to clinical trials. Currently, aside from CLN2 (ClinicalTrials.gov Identifier: NCT01907087), this knowledge seems still insufficient for most other NCL forms. The collaborative efforts that achieved this goal for the CLN2 ERT trial underline the value of compiling in a single database NCL patient natural history data available in different countries, clinics, research institutions, and families. Efforts continue to try and achieve this goal (http://www.dem-child.eu/index.php/wp03-epidemiology-natural-history.html).

To bridge our knowledge gaps in understanding the function of the wildtype CLN proteins (Cárcel-Trullols et al., this issue), a variety of organism and cell models are being used and further developed (Bond et al., this issue). Hopefully, these model systems will yield a more in-depth understanding of the disease pathomechanisms associated with different CLN disease genes and alleles. The results may also open new avenues for therapy as understanding CLN function may unmask druggable pathways that can compensate for the loss of CLN function. Results from these models will hopefully also facilitate the development of biomarkers and surrogate markers to monitor disease progression, and therapeutic effects of drugs in the clinic. Gaps in understanding CLN function also hamper the development of assays for drug discovery and target validation. The obstacles are perhaps less of an issue for ERT or gene-based therapies aimed at replacing a missing enzyme, but they seem more significant when trying to develop and test therapies for NCLs caused by mutations in transmembrane proteins. For these NCLs, ERT-based scenarios offer currently no solution, and also the outcomes of preclinical gene therapy studies trying to supply the wildtype gene have so far met with limited success (Hughes et al., this issue) [9]. More encouraging results have recently been obtained using human induced pluripotent stem (iPS)-derived cellular models for CLN3 [10,11]. It is hoped that iPS-based cellular and organoid models offer a new set of translational models that can facilitate drug discovery. Perhaps, they also offer alternatives to NCL mouse or large NCL animal models. Large NCL animal models are available but only for some of the NCLs [12], and have been instrumental to move a therapy forward to the clinic [13,14]. Mouse models are widely used in NCL research but they do not always mimic important pathophysiological aspects of human disease. Efficacy studies in mouse models can also be hampered by insufficient target engagement due to pharmacokinetic properties of drugs in this species. This should not prevent us from developing therapies that might help patients. Therefore, it is important to continue the development of alternative preclinical test systems such as human iPS-based models that can raise our confidence to propose and move new therapies forward to patients.

In summary, to push much-needed treatments to the clinic faster, it is of utmost importance to understand the critical translation-relevant research gaps for the NCLs and find solutions to bridge gaps. Funding alone is not enough to close the gaps, it also requires collaboration between all stakeholders including academic and clinical researchers, industry, patients, families, patient associations and policymakers [15]. In a joint session with patient organizations and researchers, eight teams presented their thoughts on gaps and potential solutions for bridging them. Topics discussed included large animal models, human NCL pathology and access to human tissue, rare NCLs, links to other diseases, the gap between clinic and clinical trials, working together towards a cure, palliative care, and a scientist's perspective on NCL research and career opportunities.

2. Large animal models (I. Tammen, D.N. Palmer)

The recent elegant work demonstrating efficacy of ERT in CLN2-deficient dogs exemplifies how instrumental a large animal model can be in the translation of therapies from bench-to-bedside [14]. Brain size and complexity, lifespan, and the spectrum of clinical signs are all arguments in favor of using large animal models in preclinical PoC studies. Downsides are costs, handling, ethical issues and often also the lack of natural large animal mutants for certain NCLs including CLN3, for which a genetically engineered CLN3 minipig model is in progress (http://www.exemplargenetics.com/pipeline/). Ovine models for CLN5 and CLN6 are being used to validate gene therapy-based approaches (Palmer et al., this issue). Other large animal models identified with CLN mutations include CLN1 (dog), CLN5 (dog and cattle), CLN6 (dog), CLN8 (dog), CLN10 (sheep and dog), and CLN12 (dog) [12]. The team discussed some of the difficulties encountered when trying to identify novel natural occurring CLN mutants. One hurdle is that affected animals are often deceased or unavailable for breeding and research. Other obstacles include costly autopsies, owners dislike the association with breeds of genetically deficient stock, dogs are pets, owners are often largely unaware of a need for models, and funding available to support the search and characterization of new models is scarce and difficult to obtain. However, since sequencing costs are no longer a serious barrier, the team suggested to raise more awareness amongst breeders and veterinarians, and provide both with a list of expert pathologists and geneticists they can consult. It was also suggested to invite veterinarians to future NCL meetings. At the same time it was felt that clearer inclusion criteria are needed to define NCL, as novel candidate genes will likely emerge.

3. Human NCL pathology and access to human tissue

(J.D. Cooper, H.H. Goebel).

Scientists perform treatments in disease models whereas the ultimate goal is to treat human disease. For a variety of practical and ethical reasons, one relies on cellular and animal models which are not always as informative as one would like them to be. Every single model has its strengths and weaknesses. The authors' opinion is that mouse models that genocopy a human disease can be good mechanistic models, but at the same time they frequently fail to phenocopy important pathophysiological aspects of a human disease. Hence, great care needs to be taken when interpreting findings in such models with regard to their translatability to human. For the purpose of better understanding disease onset, progression and testing therapies, large animals may offer better options because they might better phenocopy a human disease. For this reason large animal models can add great value, for testing therapies as well as for understanding disease processes. The team emphasized the huge gaps that still exist in understanding the presymptomatic phase, the onset, and the progression of human NCL pathologies. Non-invasive techniques including ophthalmological measurements, EEG and MRI are being used to try and close some of these gaps (http://www.dem-child.eu/index.php/wp03-epidemiology-natural-history.html) [16,17], as access to human tissue is difficult. The number of samples available is limited, most samples represent end-stage disease, and studies were performed years back without technologies and knowledge available today. To improve the situation, the team suggested that a coherent process should be put in place for systematic archiving of human NCL tissues in a single database. This virtual biobank should list ideally all samples available in an anonymous fashion and indicate their location as well as the key genetic and clinical information. Access to the database should be ‘open source’ for the research community and a streamlined approval process should be in place to request samples for studies. Since tissue donations are not frequent, it was also suggested to improve the tissue donation process. For example, by emphasizing the tremendous value of tissue donations to

those involved in this process (families, caretakers, clinicians) and preparing them to handle the difficult emotional aspects of this theme. It was felt that human tissue is and remains an invaluable resource to better understand the NCLs. It was recommended that a dedicated team should follow up on this theme.

4. Rare forms of NCL (S. Hofman, I. Noher)

Most rare cases of NCL are collectively caused by mutations in CLN5, CLN6, CLN7, or CLN8 while mutations in CLN10, CLN11, CLN12, CLN13, and CLN14 are extremely rare (http://www.ucl.ac.uk/ncl/SummaryTableMay2015.htm) [3]. Therapeutic routes using ERT and gene therapy are currently being investigated for the more prevalent forms CLN1 [18] and CLN2 [6,13,14] and this may help to pave the road to therapy for some of the rarer NCL forms including CLN5. Otherwise, the team seemed to agree that for the rare NCLs, the gaps in research and the challenges facing clinical translation of therapies seem similar to those for the frequent forms. These included, in particular, the lack of a unified registry database and unified clinical rating scales.

5. Links to other diseases (F.M. Platt)

The NCLs are rare diseases and research into any rare disease can greatly benefit from overlaps found with molecular mechanisms and/or therapeutic entry points discovered in other diseases. Especially (but not only) if the latter are more frequent. Examples presented by the team included overlaps identified between Parkinson's disease (PD) and Gaucher disease, as well as overlaps between Niemann–Pick type C (NPC), Tangier, Smith–Lemli–Opitz syndrome (SLOS) and Tuberculosis [19]. These links have been discovered on the basis of clinical observations and genetic screens (PD and Gaucher), or on the basis of cellular phenotypes (NPC e.a.). The general consensus was that finding links between NCLs and other diseases requires more in-depth knowledge of CLN gene function and pathogenic mechanisms. Adding on a few examples beyond those mentioned by the team: heterozygous and homozygous mutations in CLN11 are associated with frontotemporal lobe degeneration (FTLD) and NCL, respectively [20], autosomal recessive mutations in CLN12 are associated with Parkinsonism [21], and cathepsin D deficiency (CLN10) is associated with α-synuclein accumulation as seen in idiopathic and familial forms of PD [22]. For CLN3, mutations have recently been associated with autophagic vacuolar myopathy [23]. Of particular interest are also non-syndromic mutations in CLN genes associated with retinal disease in patients without NCL [24,25]. Such novel mutants will hopefully spur NCL research, provide new ideas for therapy, and facilitate understanding CLN-function and pathomechanisms.

6. Bridging gaps between clinic and clinical trials (H. Adams, A. Schulz)

The team re-emphasized that in the early clinical phase, new drugs and treatments have to meet the criteria including safety and tolerability. In addition, preliminary evidence of what dose is needed for efficacy is a desirable goal at the earliest clinical stage. It was discussed that one of the challenges in NCL research is how to best gather and use clinical information, that can inform on primary and secondary outcomes, and that can define outcomes that can realistically be targeted and achieved in a clinical trial. This is particularly challenging in diseases like the NCLs because trials can only be performed in low numbers of patients. Questions like trial design and how to conduct a rigorous trial are immediately eminent as outcomes should point at truly transformative benefits for the patient. It was also emphasized that it is important to keep in mind what is of prime importance to the patient. For example, in CLN3 disease loss of vision is typically the first debilitating change patients face and it greatly impacts their quality of life including social and learning capabilities, usually well before other CLN3-associated cognitive disturbances emerge. Therefore, the benefits of early treatments that primarily block or delay retinal degeneration should not be underestimated.

Ideally, clinical observations and data gathered should help guide and define hypothesis-driven, meaningful clinical endpoints. The team stressed that it is also important that clinical investigators and patients have a common understanding of what is feasible and acceptable from the patient's point of view. The number of patients participating in trials will always be low but investigators and clinicians nonetheless face the difficult task to define proper inclusion/exclusion criteria for taking patients into a trial. Regarding the trial itself, there was a clear recommendation for scenarios that combine excellent standard clinical care and clinical research. Achieving this can be challenging because patients participating in trials often come from geographically distant regions while maintaining the highest standard of care during the trial might require extended hospitalization and monitoring by a local highly specialized team. It was also emphasized that once proof-of-concept in patients has been achieved, challenges should not be underestimated to expand and confirm findings in a larger and perhaps clinically more diverse patient population.

7. Working together towards a cure (S.E. Mole, H. Band)

The NCLs are rare (http://www.ucl.ac.uk/ncl/index.shtml) [3] and altogether, they make up for only a small number of all patients affected by the thousands of rare genetic diseases known today (http://www.orpha.net/orphacom/cahiers/docs/GB/List_of_rare_diseases_in_alphabetical_order.pdf). Taken together, rare diseases account for a significant proportion of patients suffering from chronic diseases and the associated socio-economic burden (http://www.irdirc.org/). To improve this situation, the International Rare Disease Consortium has a goal to deliver 200 new therapies by the year 2020. It is hoped that these will include also one or more NCLs. Within the European Union (EU) there has been a long-standing focus to foster collaborative working models in the rare disease field. Special emphasis lies on collaborative working models that are cross-sectional and include basic scientists in academia, clinicians, biotechs and/or pharma, as well as patient organizations. Endeavors in the NCL field include the EU funded the DEM-CHILD project (http://www.dem-child.eu/index.php/background-16.html) which is coming to completion. Also, a new European collaborative consortium (BATCure) has been assembled and a proposal submitted in the context of the Horizon 2020 call PHC-14-2015.

8. Palliative care (M. Frazier, A. West)

The team gave the following interpretation of what palliative care means to the Batten disease community: “a holistic, multi-disciplinary approach that enables someone with an NCL diagnosis and their family to live a life that is the best it can be”. A priory, this requires early diagnosis which in many countries is not state-of-the-art. Even in countries where the diagnostic tools are available, it often takes years before a proper diagnosis is established. Therefore, general awareness and focused educational programs targeting those that could facilitate early diagnosis (e.g. ophthalmologists) are desirable and this strategy is actively pursued by NCL foundations. It was mentioned that contributions of families keep changing the landscape of supportive research and care. Nonetheless, questions were raised how to further improve socio-cultural, payment and access support for patients and their families. In a broader context of neurodegenerative diseases, the question was also asked how we can accelerate more holistic social science research to improve care for children with such devastating diseases. Towards this goal, one area the team identified for further development was to better define and communicate in the global NCL community which current assets are available. For example, with respect to best practice in palliative care (including initial family engagement), day-to-day care, communication, hospice provision, and end-of-life care. Support organizations including the Batten Disease Support and Research

Association (BDRSA) and the Batten Disease Family Association (BDFA) seem ideally positioned to foster further progress in these areas.

9. Junior scientist's perspective on NCL research and career (M. Bond)

Many junior NCL scientists, after finishing their PhD or a postdoc in the NCL field, eventually move on to other areas of research. Rewards, career and funding opportunities are greater in larger and popular research fields covered by many laboratories and provide junior scientists with more options, flexibility and continuity in their research careers. Many of the difficulties postdocs and junior scientists face on their way to establish an independent career in academia have recently been summarized [26]. To help researchers continue in the NCL field, it was felt that transition grants might be one way to help scientists bridge this critical phase in their career. The wish was also expressed to improve sharing of knowledge and tools in the NCL community. Some also felt that new students might be attracted to NCL research by making available a comprehensive educational data package that covers basic research and clinical data.

In conclusion, to successfully bring therapies to the patients we need to bridge existing gaps in NCL research and a short list of recommendations proposed at this meeting is shown below. Bridging gaps is best accomplished by fostering and embracing collaborative interdisciplinary efforts involving all stake holders. Raising more general awareness and providing educational programs should further support these efforts to facilitate early diagnosis, family planning, and improve palliative care and treatment.

Short list of recommendations

- Raise awareness amongst veterinarians and breeders of the great value of large animal models, and help them to identify new models by providing a list of expert pathologists and geneticists for consultation.
- Establish an “open source” virtual biobank listing ideally all worldwide available NCL tissue samples, and improve the tissue donation process.
- Merge available patient registries in a single database, and unify registry standards and rating scale standards.
- Identify clinically meaningful measures and outcomes.
- Try to establish links between NCLs and other diseases.
- Provide educational programs to ophthalmologists and medical doctors to facilitate early diagnosis.
- Communicate in global NCL community the assets available to help patients and their families.
- Foster funding scenarios for young researchers enabling them to progress and pursue independent careers in NCL research.
- Foster and embrace collaborative interdisciplinary efforts involving all stake holders.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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